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Cite this as: *BMJ* 2024;386:q1841
http://dx.doi.org/10.1136/bmj.q1841

SGLT-2 inhibitors and dementia

New evidence links these agents to lower dementia risk in adults with type 2 diabetes

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Dementia remains a profound global health challenge. According to a report from the World Health Organization, more than 55 million people worldwide currently have dementia, and each year the disease is diagnosed in around 10 million people.[1] This neurological disorder, characterised by the progressive deterioration of cognitive function, continues to elude effective treatment. Notably, type 2 diabetes is recognised as an important modifiable risk factor for dementia, contributing to both Alzheimer's disease and vascular dementia.[2] Recent evidence suggests that certain antidiabetic drugs, specifically sodium-glucose cotransporter-2 (SGLT-2) inhibitors, may offer neuroprotective benefits beyond their glucose lowering effects, thereby adding a promising dimension to dementia prevention strategies.[3-5]

The linked study by Shin and colleagues (doi:10.1136/bmj-2024-079475) sheds light on this potential benefit by analysing data from the Korean National Health Insurance Service.[6] These authors compared the risk of dementia associated with SGLT-2 inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors in 110 885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years. The study included those starting treatment with an SGLT-2 inhibitor who had a considerably lower incidence of dementia than those starting treatment with a DPP-4 inhibitor, over a mean follow-up of 670 days (0.22 *v* 0.35 per 100 person years; hazard ratio 0.65, 95% confidence interval (CI) 0.58 to 0.73). These findings indicate a 35% relative reduction in overall dementia risk among SGLT-2 inhibitor users.

The risk reduction associated with SGLT-2 inhibitors was consistently observed across different types of dementia, including Alzheimer's disease (hazard ratio 0.61, 95% CI 0.53 to 0.69) and vascular dementia (0.48, 0.33 to 0.70). Additionally, the effect seemed more pronounced with longer treatment duration. These findings extend current knowledge about the potential pleiotropic effects of SGLT-2 inhibitors on neurodegenerative diseases, in addition to their known metabolic and cardiorenal benefits.[7]

Shin and colleagues successfully showed how to use a large scale secondary healthcare database to explore clinically important questions that have yet to be evaluated or are difficult to evaluate through randomised controlled trials. The authors used rigorous pharmacoepidemiological approaches, such as applying a target trial emulation framework,[8] using an active comparator new user design,[9] and utilising propensity score methods to control for confounders.[10] These methods helped avoid biases common to observational studies, thereby strengthening the ability to draw causal inference from observational data.[8] Various subgroup analyses and sensitivity analyses, along with positive and negative control outcome analyses, also support the robustness of the study findings.

The possible mechanisms driving the lower risk of dementia observed with SGLT-2 inhibitors are multifaceted. SGLT-2 inhibitors reduce hyperglycaemia, improve insulin resistance, decrease oxidative stress and inflammation, and provide cardiovascular and renal benefits, all of which are key contributors to the development of dementia in adults with type 2 diabetes.[4 5] Additionally, preclinical studies have suggested that SGLT-2 inhibitors are linked to the amelioration of amyloid β deposition and tau protein phosphorylation, which are considered major pathogenetic mechanisms of Alzheimer's disease.[4 5]

Some limitations of Shin and colleagues' study should be noted. Several factors, such as participants' serum glucose levels, disease severity, over-the-counter drug use, and lifestyle behaviours, were not included in the analyses, leaving the possibility of residual or unmeasured confounding. In addition, the relatively short mean follow-up period of 670 days may make this study susceptible to informative censoring, reverse causation, and outcome misclassification, potentially leading to overestimation of the results.

Shin and colleagues' findings have important implications for clinical practice as well as from a public health perspective. For people with type 2 diabetes, the potential reduction in dementia incidence with SGLT-2 inhibitor treatment offers important additional clinical benefits beyond the known glucose lowering effects and other cardiorenal protections. For clinicians, these findings emphasise the need to integrate considerations about cognitive health into diabetes management strategies, potentially supporting early use of SGLT-2 inhibitors for people at risk of dementia.

For researchers, the new findings indicate a need for randomised controlled trials to confirm these observational results. Additional studies are also needed to explore the underlying mechanisms of any neuroprotective effects of SGLT-2 inhibitors. Clinical guidelines and healthcare policies should be updated regularly to incorporate latest best evidence on the potential benefits of SGLT-2 inhibitors, including reduced dementia risk, given the substantial socioeconomic and public health burdens associated with both dementia and type 2 diabetes.

As no cure currently exists for dementia and few effective treatment options are available, strategies that can potentially prevent onset are critically important. Although further randomised controlled

trials are urgently needed to confirm these findings, Shin and colleagues' study reports promising results and suggests a possible repurposing of SGLT-2 inhibitors for dementia prevention in people with type 2 diabetes.

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: None.

Further details of The BMJ policy on financial interests is here: https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf.

Provenance and peer review: Commissioned; not externally peer reviewed.

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